

# Systematic Review of Health Outcomes in Relation to Salt Intake Highlights the Widening Divide Between Guidelines and the Evidence

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Until recently, the salt debate remained dominated by a select group of highly vocal global leaders whose goal is to impose their views through an unbalanced interpretation of so-called compelling evidence. Sailing against the tide, in this issue of the Journal, Graudal and colleagues published a comprehensive review of the literature<sup>1</sup> that complied with the highest possible quality standards as proposed by the Meta-analysis of Observational Studies in Epidemiology group.<sup>2</sup> Data from 23 cohort studies and 2 follow-up studies of randomized controlled trials ( $n = 274,683$  participants) showed that the risks of all-cause mortality or cardiovascular disease were higher at low and high vs. usual sodium intake, congruent with a U-shaped association between health outcomes and salt intake.<sup>1</sup> The hazard ratios of total mortality and cardiovascular disease for low vs. usual sodium intake were 1.10 (95% confidence interval (CI) = 1.01–1.22) and 1.11 (95% CI = 1.01–1.22), respectively. The corresponding hazard ratios for high vs. usual sodium exposure were 1.16 (95% CI = 1.03–1.30) and 1.12 (95% CI = 1.02–1.24).<sup>1</sup>

## Cardiovascular endpoints and 24-hour urinary sodium

Graudal *et al.*'s findings are in line with our cohort study in European populations published in 2011.<sup>3</sup> Nearly 90% of the world's populations have a mean usual sodium intake ranging from 115 to 215 mmol per day.<sup>4</sup> This range nearly corresponds with the mean values of 24-hour urinary sodium excretion in the low (107 mmol) and high (260 mmol) thirds of the distribution in European populations.<sup>3</sup> Moreover,

Graudal *et al.* reported that in population-representative samples adjusted for multiple confounders the risk of all-cause mortality was higher at low vs. usual sodium intake but not at high vs. usual sodium intake, with hazard ratios of 1.16 (95% CI = 1.09–1.23) and 0.96 (95% CI = 0.84–1.10), respectively.<sup>1</sup> Among our 3,681 participants followed up for a median 7.9 years, all-cause mortality was not related to urinary sodium, but cardiovascular mortality decreased across increasing tertiles of 24-hour urinary sodium excretion, from 50 deaths in the low excretion group, to 24 in the medium excretion group (mean = 168 mmol), to 10 in the high excretion group, resulting in respective death rates of 4.1%, 1.9%, and 0.8%. In multivariable-adjusted analyses, this inverse association retained significance ( $P = 0.02$ ); the hazard ratios expressing the risk of a cardiovascular death in the low, medium, and high tertiles were 1.56, 1.05, and 0.96, respectively ( $P$  for linear trend = 0.02).<sup>3</sup> Among 2,096 participants followed up for 6.5 years, the risk of hypertension did not increase across increasing tertiles ( $P = 0.93$ ).<sup>3</sup> In 1,499 participants followed up for 6.1 years, systolic blood pressure increased by 0.37 mm Hg per year ( $P < 0.001$ ), whereas sodium excretion did not change ( $-0.45$  mmol per year;  $P = 0.15$ ). In multivariable-adjusted analyses, a 100-mmol increase in sodium excretion was associated with a 1.7-mm Hg increase in systolic blood pressure ( $P < 0.001$ ) with no difference in diastolic blood pressure.<sup>3</sup> The systolic estimate approximated to the effects associated with a 75-mmol change in 24-hour urinary sodium in meta-analyses of sodium intervention studies in normotensive subjects, reportedly ranging from 2.0 mm Hg<sup>5</sup> to 2.4 mm Hg.<sup>6</sup>

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Even before our article<sup>3</sup> was brought out in print, *The Lancet* found it necessary to publish an unsigned editorial warning that our study was flawed.<sup>7</sup> The editorial cited Peter Briss, a medical director of the US Centers for Disease Control and Prevention, who qualified our study as being small with low event rates and relatively young participants.<sup>7</sup> Walter Willett, Chair of the Department of Nutrition at Harvard School of Public Health, also pointed out other weaknesses—unreliable measurement of sodium intake, failure to account for key factors that influence sodium intake and heart disease risk, and missing or incomplete urine data from large numbers of participants.<sup>7</sup> We answered these criticisms in the correspondence section of the *Journal of American Medical Association*.<sup>8</sup> As reviewed elsewhere<sup>9</sup> and in keeping with Graudal *et al.*'s meta-analysis,<sup>1</sup> several studies subsequently noticed an inverse association or a J-shaped relation between mortality<sup>10,11</sup> or cardiovascular disease<sup>12,13</sup> and urinary sodium. Nevertheless, we and other investigators remained the target of heavy flak.<sup>14–16</sup> On the other hand, we also received letters of support from several experts in the field.<sup>17</sup>

# Review of the “compelling” evidence

*The Lancet* went on to state that our study was disappointingly weak and contributed little to the understanding of salt and disease.<sup>7</sup> It was likely to confuse public perceptions of the importance of salt as a risk factor for high blood pressure, heart disease, and stroke. Questions of intervention and outcome, such as sodium intake and cardiovascular disease events, cannot be answered by small observational studies. We therefore found it useful to read beyond the abstract of some of the papers that are part of the so-called compelling evidence supporting a drastic reduction of salt intake in the general population below the current usual level of 115–215 mmol per day.<sup>4</sup> In INTERSALT, the within-center analyses demonstrated an inconsistent association between systolic blood pressure and 24-hour urinary sodium excretion, with both significantly positive and inverse associations.<sup>18</sup> The between-center analysis showed an effect size of 7.1 mm Hg per 100 mmol sodium across 52 centers ( $P < 0.001$ ), which weakened to 2.8 mm Hg per 100 mmol after exclusion of 4 primitive societies with extreme low urinary sodium output.<sup>18</sup> Notably, the methodology to collect 24-hour urine samples was similar in INTERSALT<sup>18</sup> and in our population studies,<sup>3,19</sup> and the average values of 24-hour urinary sodium were similar in our studies<sup>3,19</sup> and the Belgian (Gent and Charleroi), Polish (Kraków), and Russian (Novosibirsk) INTERSALT centers.<sup>20</sup> Moreover, the between-center INTERSALT analysis is an aggregate-level ecological meta-analysis that is vulnerable to demonstrating spurious associations.<sup>21,22</sup> A Finnish population study with a sample size ( $n = 2436$ ), smaller than ours is part of the compelling evidence.<sup>23</sup> In the summary of their article,<sup>23</sup> the authors concluded: “High sodium intake predicted mortality and risk of coronary heart disease, independent of other cardiovascular risk factors, including blood pressure. These results provide direct evidence of the harmful effects of high salt intake in the adult population.” However, among 1,263 women, none of the fully adjusted hazard ratios relating

fatal outcomes, coronary heart disease, or stroke to 24-hour urinary sodium reached significance.<sup>23</sup> Among 1,173 men, the hazard ratios were significant for fatal outcomes and coronary heart disease but not for stroke, the complication of hypertension most closely related to blood pressure.<sup>24</sup> Moreover, subgroup analyses demonstrated that the association between mortality and 24-hour urinary sodium reached significance only among 514 obese men,<sup>23</sup> whereas for women no analysis stratified for body mass index was reported.

Yang and colleagues analyzed 12,267 adults included in the Third National Health and Nutrition Examination Survey Linked Mortality File (1988–2006).<sup>25</sup> The abstract closed by stating that a higher sodium-to-potassium ratio was associated with a significantly increased risk of cardiovascular disease and all-cause mortality. However, in multivariable-adjusted analyses, the risk of cardiovascular mortality ( $n = 825$ ) and death from ischemic heart disease ( $n = 443$ ) was not significantly associated with usual sodium intake but was inversely related with potassium ingestion, explaining the positive correlation with the sodium-to-potassium ratio. With adjustments applied, all-cause mortality ( $n = 2,270$ ) was positively associated with usual sodium intake but inversely associated with potassium consumption, suggesting that not cardiovascular disease or blood pressure, but instead noncardiovascular mortality, could have driven the association between total mortality and usual sodium intake.

The investigators of the Trial of Nonpharmacologic Interventions in the Elderly (TONE) also contributed to the compelling evidence. They enthusiastically concluded that the TONE results had important implications both for public health professionals and clinical practitioners.<sup>26</sup> They proposed that older patients with hypertension were able to make and sustain lifestyle changes and that these “impressive” results were obtained in the context of moderate reductions in sodium consumption.<sup>26</sup> However, 8,787 patients had to be screened to randomize a highly selected group of 11.1%.<sup>26</sup> The reduction in 24-hour urinary sodium in participants assigned to salt restriction averaged approximately 40 mmol/day (920 mg/day), resulting in a decrease in blood pressure averaging 3.5 mm Hg systolic and 1.9 mm Hg diastolic. Furthermore, sodium restriction reduced the risk of a primary endpoint by 31%, but the primary endpoint consisted mainly of weak outcomes, such as high blood pressure after discontinuation of antihypertensive drugs, resuming antihypertensive drug treatment, and inability to withdraw blood pressure-lowering treatment. There was no significant between-group difference in what really matters, the occurrence of cardiovascular complications, such as angina, myocardial infarction, stroke, or coronary revascularization ( $P \geq 0.16$ ).<sup>26</sup> However, a similar trend of a lower incidence of adverse health outcomes was observed in the follow-up of Trials of Hypertension Prevention (TOHP) I and II participants randomized to a reduction of sodium intake or usual care.<sup>27</sup>

In a meta-analysis of studies relating cardiovascular outcomes to sodium intake, Strazzullo and colleagues concluded in the summary: “High salt intake is associated with significantly increased risk of stroke and total

cardiovascular disease.”<sup>28</sup> The risk of stroke increased by 6% (95% CI = 3%–10%;  $P = 0.04$ ) for an increase in sodium intake by 50 mmol per day.<sup>28</sup> A similar trend for cardiovascular disease was not significant (19%; 95% CI = –31% to 107%;  $P = 0.53$ ). Across the reports included in Strazzullo’s meta-analysis, the methods for assessing salt intake were not standardized.<sup>29</sup> Studies with exclusively fatal outcomes were pooled with those including both fatal and nonfatal events. Moreover, the hazard ratios used in the variance-weighted meta-regression analysis were not standardized to the same amount of sodium.<sup>29</sup> In contrast with Graudal *et al.*,<sup>1</sup> Strazzullo and colleagues compared the highest category with the lowest category, assuming a linear association over the whole range of sodium intake.<sup>28</sup>

The long-term observational follow-up of TOHP I and II<sup>27,30,31</sup> also generated compelling evidence. In the most recent report, among 2,275 prehypertensive TOHP participants characterized by a median of 5 24-hour urine collections (range = 1–7), 193 cardiovascular events occurred.<sup>31</sup> First events included 68 myocardial infarctions, 77 coronary revascularizations, 22 strokes, and 27 cardiovascular deaths.<sup>31</sup> In fully adjusted models accounting for clinic, treatment assignment, demographic variables, baseline covariables, and changes in weight, smoking, and exercise, there was a nonsignificant trend of increasing risk with higher sodium excretion. Compared with those with sodium excretion ranging from 3,600 mg/day (157 mmol/day) to 4,800 mg/day (209 mmol/day), the risk for those with sodium <2,300 mg/d was 32% lower ( $P = 0.13$ ). When sodium was considered as a continuous term, risk increased by 17% per 1,000 mg/day (43 mmol/day) increase in sodium, but as for the categorical analysis, the  $P$  value did not reach formal significance ( $P = 0.054$ ).<sup>31</sup> The compelling evidence in the TOHP report<sup>31</sup> was therefore based on nonsignificant or borderline  $P$  values.

### The Institute of Medicine assessment

Statistical modeling led to the belief that modest reductions in dietary salt intake could substantially reduce cardiovascular events and medical costs.<sup>32,33</sup> Short-term intervention studies in human normotensive volunteers<sup>5,6</sup> or hypertensive patients<sup>5,6</sup> or even chimpanzees<sup>34</sup> cannot be reasonably extrapolated to the long-term exposure of the general population to salt. The recent Institute of Medicine (IOM) report, “Sodium Intake in Populations: Assessment of Evidence,”<sup>35</sup> failed to find robust evidence to support current guidelines promoted by the US Centers for Disease Control and Prevention,<sup>36</sup> the New York City Department of Health and Mental Hygiene,<sup>37</sup> or the American Heart Association<sup>38</sup> to reduce sodium intake population-wide from the current 3,400 mg/day (148 mmol/day) to <2,300 mg/day (100 mmol/day) and, for half of the US population at increased cardiovascular risk, to <1,500 mg/day (65 mmol/day). The IOM recognized heterogeneity of results among observational and experimental studies, baseline level of blood pressure and sodium intake being the major determinants of the blood pressure responses to sodium restriction.<sup>35</sup> Furthermore, the IOM cautioned against sodium intakes <1,500 mg/day

(65 mmol/day).<sup>35</sup> Of US adults, only 9% currently consume <2,300 mg/day and just 0.6% have a sodium intake <1,500 mg/day,<sup>39</sup> rendering the ban on salt,<sup>38</sup> if at all feasible,<sup>4</sup> the most aggressive lifestyle intervention ever planned in the history of mankind. These low-salt goals should be reached by 2020<sup>40</sup> without being substantiated by large randomized clinical trials proving benefit in terms of hard cardiovascular outcomes and without questioning feasibility and acceptance by the general public. The guidelines<sup>36–38</sup> thereby completely disregard potential harm caused by the exponential activation of the renin-angiotensin-aldosterone system<sup>41</sup> and the sympathetic nervous system<sup>42</sup> by adverse changes in serum lipids<sup>43</sup> or by increasing insulin resistance<sup>44</sup> once 24-hour urinary sodium excretion drops to <100 mmol/day. The activation of sodium conserving mechanisms at intakes <100 mmol/day<sup>41–43</sup> and the strong dependence of any blood pressure responses on the baseline level<sup>45</sup> make a linear dose–response curve as postulated by the guidelines<sup>38</sup> or extrapolations<sup>32,33</sup> unlikely. Graudal *et al.*’s meta-analysis, in fact, showed a U-shaped relation.<sup>1</sup> The meta-analysis included NHANES I<sup>46</sup> and III<sup>47</sup> data. Substituting the NHANES data used by Graudal *et al.*<sup>1</sup> with more recent analyses published by other investigators<sup>25,48</sup> resulted in a relative risk of total mortality for low vs. usual sodium of 1.01 (95% CI = 0.90–1.14). However, the number of participants retained in the analyses ( $n = 11,346$  vs.  $n = 9,485$ )<sup>46,48</sup> and the number of deaths ( $n = 3,923$  vs.  $n = 2,486$ )<sup>46,48</sup> were higher in the first compared with the repeat analysis of NHANES I, whereas the opposite was the case for the first compared with the repeat analysis of NHANES III (participants analyzed: 8,699 vs. 12,267; deaths: 1,150 vs. 2,270; follow-up: 8.7 vs. 14.8 years).<sup>25,47</sup> Graudal *et al.*’s meta-analysis did not include the TOHP cohort observational analysis<sup>31</sup> published online in January 2014 and in print 3 months later.

Several publications authored by experts at the other side of salt debate, including a semiquantitative review,<sup>15</sup> highlighted the challenges of interpreting observational reports on the relation between cardiovascular disease and salt intake. However, for now, in the absence of randomized clinical trials powered to study the long-term cardiovascular health outcomes in relation to different levels of salt intake, observational studies remain a major source of information in spite of possible pitfalls.<sup>15</sup> Expert committees writing salt guidelines<sup>36–38</sup> argue that all relevant research should be considered and weighed appropriately, in particular the intervention studies in normotensive<sup>5,6</sup> and hypertensive<sup>5,6</sup> volunteers and the mainly observational<sup>28</sup> and ecological<sup>18,49</sup> studies showing association between stroke and salt intake.

### Conclusions

Graudal *et al.*’s meta-analysis solidifies the evidence from previous studies<sup>3,10–13</sup> and extends the IOM report<sup>35</sup> by identifying a specific range of sodium intake (2,645–4,945 mg/day) associated with the most favorable health outcomes—within which variation in sodium intake is not associated with variation in mortality. Moreover, this optimal range of intake, based upon currently available evidence, is corresponding with the dietary intake of most of the world’s populations<sup>3,4,50</sup> and is in accordance with the



IOM rules for definition of an adequate sodium intake and an upper tolerable sodium level.<sup>51</sup> For science to advance, from time-to-time, medical textbooks and dogma's need a Copernican revolution. Perhaps the time has come for the advocates of the worldwide action on salt to reconsider their salt-centric point of view of the healthcare cosmos. A similar paradigm shift in the management of compensated<sup>52</sup> and decompensated<sup>53,54</sup> heart failure is currently unfolding.

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# DISCLOSURE

The authors declared no conflict of interest.

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